AMENDMENTS TO THE SPECIFICATION:

On page 1, after the title, please insert the following new paragraph as follows:

This application is a National Stage Application of PCT/JP2004/014378, filed September 30, 2004.

Please amend paragraph [0023] as follows:

[0023] According to the present invention, a method of identifying a compound that inhibits the degradation by HtrA2 of at least one of SHC3, ATF6 and CREBL1 can be also carried out. The compound obtained by the identification method can be used for inhibiting cell death (for example, neural cell death), ~~diabetes,~~ and for preventing, treating, or controlling a disease accompanied with cell death (such as brain ischemia and neurodegenerative diseases).

Please amend paragraph [0052] as follows:

[0052] All of HtrA2, SHC3, ATF6, and CREBL1 are known proteins and disclosed in GenBank with the accession numbers NM_013247, ~~NM_06848~~ NM_016848, NM_007348, and ~~NM_00438~~ NM_004381 respectively.

Please amend paragraph [0053) as follows:

[0053] The amino acid sequence of HtrA2 used in the Examples is shown in SEQ ID NO: 4. The nucleotide sequence of HtrA2 DNA encoding the amino acid sequence set forth in SEQ ID NO: 4 is shown in SEQ ID NO: 3. The polypeptide shown by the amino acid sequence set forth in SEQ ID NO:4 is a mature HtrA2. The mature HtrA2 denotes a mature protein that is generated from HtrA2 precursor protein (SEQ ID NO: 2) by cleavage of its N-terminal 133

amino acid residues and has a protease activity. Hereinafter, the HtrA2 with protease activity may be referred to as an active HtrA2. Further, a protein (SEQ ID NO: 8, which may be referred to as mature HtrA2 (ΔAVPS)) that lacks the N-terminal four amino acid residues (AVPS) in the mature HtrA2, or a protein (SEQ ID NO: 10, in some cases referred to as mature HtrA2 (GVPS)) with the substitution of alanine among the N-terminal four amino acid residues of the mature HtrA2 with glycine may be used as active HtrA2. Such HtrA2 with an introduced mutation can be used as active HtrA2 since there is no change in the protease activity. In the meantime, HtrA2 without protease activity may be in some cases referred to as inactive HtrA2. The inactive HtrA2 may be, for example, HtrA2 mutant without protease activity resulting from a mutation of the amino acid residue at the site necessary for protease activity of HtrA2 in the amino acid sequence of HtrA2. The site necessary for protease activity of HtrA2 includes a protease activity domain, more preferably the 174th serine residue of mature HtrA2 (SEQ ID NO: 4) (which is corresponding to the 306th residue of the precursor protein (SEQ ID NO: 2)). More specifically, the inactive HtrA2 can be, for example, HtrA2 mutant (SEQ ID NO: 6, which may be referred to as mature HtrA2 (S306A)) with a substitution of the 174th serine residue of mature HtrA2 (which is corresponding to the 306th residue of the precursor protein (SEQ ID NO: 2)) with alanine. Further, a protein (SEQ ID NO: 12, in some cases referred to as mature HtrA2 (S306A, ΔAVPS)) that lacks the N-terminal four amino acid residues (AVPS) in the mature HtrA2 (S306A), or a protein (SEQ ID NO: 14, in some cases referred to as mature HtrA2 (S306A, GVPS)) with the substitution of alanine among the N-terminal amino four amino acid residues of the mature HtrA2 (S306A) with glycine may be used as inactive HtrA2.

Please amend paragraph [0054] as follows:

[0054] The amino acid sequence of SHC3 used in the Examples is shown in SEQ ID NO: 16. Hereinafter, SHC3 protein shown by the amino acid sequence set for in SEQ ID NO: 16 may be sometimes referred to SHC3 (p64). The nucleotide sequence of SHC3 (p64) DNA is shown in SEQ ID NO: 15. It was found that the nucleotide sequence set for in SEQ ID NO: 15 had a difference in six nucleotides compared with the nucleotide sequence of SHC3 disclosed in accession number ~~NM_01648~~ NM_016848 (see Example 2). In addition, SHC3 (p52) that is a splicing variant of SHC3 was used in the present invention. SHC3 (p52) is a protein that is translated from the second ATG (360 bases down stream from the first ATG) within the coding region of SHC3 gene.

Please amend paragraph [0056] as follows:

[0056] The amino acid sequence of CREBL1 used in the Examples is shown in SEQ ID NO: 18. Furthermore, the nucleotide sequence of CREBL1 DNA is shown in SEQ ID NO: 17. It was found that the nucleotide sequence set forth in SEQ ID NO: 17 had a difference in one nucleotide compared with the nucleotide sequence of CREBL1 disclosed in accession number ~~NM_00438~~ NM_004381 (see Example 2).

Please amend paragraph [0095] as follows:

[0095] Then, CREBL1 gene was amplified by PCR and cloned into pCR-BluntII-TOPO vector. The PCR was carried out using the CREBL1 gene cloned into pCMV-Tag 5 as a template, ATF6-NF1 primer (with BamHI site instead of ATG, SEQ ID NO: 29), ATF6-NR1 primer (with XhoI site following to termination codon, SEQ ID NO: 30), and KOD-plus as DNA

polymerase. The nucleotide sequence was determined by the sequencer. It was found that the nucleotide sequence obtained in this example had a difference in one nucleotide (T450C) compared with the nucleotide sequence of CREBL1 that had already been registered in GenBank with accession number ~~NM_00438~~ NM_004381. There is no change in the amino acid resulting from this difference. In the meantime, the termination codon was changed from TGA to TAA. It was confirmed that these differences were not due to PCR errors. The nucleotide sequence of CREBL1 DNA obtained in this example and the amino acid sequence encoded by the DNA are shown in SEQ ID NO: 17 and SEQ ID NO: 18, respectively. Animal cell expression plasmid for CREBL1 was prepared by digesting the cloned CREBL1 gene with BamHI and XhoI, and then integrated it into pCMV-Tag 3.